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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/699,030	10/26/2000	Shiy Kumar	030516.0029CON1	3324

7590 03/07/2002

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EXAMINER
FREDMAN, JEFFREY NORMAN

ART UNIT	PAPER NUMBER
1637	6

DATE MAILED: 03/07/2002

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary

Application No.	Applicant(s)
09/699,030	Kumar et al
Examiner	**Art Unit**
Jeffrey Fredman	1637

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *three* MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136 (a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1) ☒ Responsive to communication(s) filed on *Oct 2, 2001* .

2a) ☐ This action is **FINAL.** 2b) ☒ This action is non-final.

3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11; 453 O.G. 213.

Disposition of Claims

4) ☒ Claim(s) *1-17* is/are pending in the application.

4a) Of the above, claim(s) *14-17* is/are withdrawn from consideration.

5) ☐ Claim(s) _____ is/are allowed.

6) ☒ Claim(s) *1-13* is/are rejected.

7) ☐ Claim(s) _____ is/are objected to.

8) ☐ Claims _____ are subject to restriction and/or election requirement.

Application Papers

9) ☐ The specification is objected to by the Examiner.

10) ☐ The drawing(s) filed on _____ is/are objected to by the Examiner.

11) ☐ The proposed drawing correction filed on _____ is: a) ☐ approved b) ☐ disapproved.

12) ☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. § 119

13) ☐ Acknowledgement is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d).

a) ☐ All b) ☐ Some* c) ☐ None of:

1. ☐ Certified copies of the priority documents have been received.
2. ☐ Certified copies of the priority documents have been received in Application No. _____ .
3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

*See the attached detailed Office action for a list of the certified copies not received.

14) ☐ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. § 119(e).

Attachment(s)

15) ☒ Notice of References Cited (PTO-892)
16) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
17) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s). _____
18) ☐ Interview Summary (PTO-413) Paper No(s). _____
19) ☐ Notice of Informal Patent Application (PTO-152)
20) ☐ Other:

DETAILED ACTION

Election/Restriction

1. Applicant's election without traverse of Group I, claims 1-13, in Paper No. 6 is acknowledged.

Priority

2. Applicant has not complied with one or more conditions for receiving the benefit of an earlier filing date under 35 U.S.C. 120 as follows:

> An application in which the benefits of an earlier application are desired must contain a specific reference to the prior application(s) in the first sentence of the specification (37 CFR 1.78).

Sequence Rules

3. This application contains sequence disclosures that are encompassed by the definitions for nucleotide and/or amino acid sequences set forth in 37 CFR 1.821(a)(1) and (a)(2). However, this application fails to comply with the requirements of 37 CFR 1.821 through 1.825 because there is no CRF and because the sequence in figure 1 is not in the paper copy of the Sequence Listing. A complete response to this action will require compliance with the Sequence Rules.

Claim Rejections - 35 USC § 112

4. Claims 10 is rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

It is vague and indefinite what is meant by "the compound of formula II, II, IV or V" in claim 10 since multiple formulas are recited. It is suggested that the word "the" be amended to "a" in order to clarify this claim.

Double Patenting

5. Because parent application 09/018,695 is indicated as abandoned, no double patenting rejection will be made. Should that application be revived by Applicant, it would require a double patenting rejection necessitated by Applicant's amendment.

Claim Rejections - 35 USC § 102

6. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless --
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

7. Claims 1-13 are rejected under 35 U.S.C. 102(b) as being anticipated by Kumar et al (WO 99/40223).

Kumar teaches the limitations of claims 1-13 (see pages 23-29, claims 1-13).

Claim Rejections - 35 USC § 103

8. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person

having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(f) or (g) prior art under 35 U.S.C. 103(a).

9. Claims 3 and 9 are rejected under 35 U.S.C. 103(a) as being unpatentable over Evangelista et al (Anal. Biochem. (1996) 235:89-97)

Evangelista teaches a compound of formula (I) (A-B-C) with a cyanine dye which meets the structural requirements of A, a linker of more than 10 atoms in length as required by B, and attached to the 5 position of dUTP, which has a triphosphate attached (page 91, figure 1). It should be noted, that because the attachment is at the 5 position, dUTP and dTTP yield identical structures.

Evangelista does not teach a structure where this compound is a dideoxynucleotide.

It would have been *prima facie* obvious to one having ordinary skill in the art at the time the invention was made to modify the labeled deoxynucleotide of Evangelista into a dideoxynucleotide since Evangelista notes "Fluor-labeled deoxynucleotide triphosphates (dNTPs) or dideoxynucleoside triphosphates (ddNTPs) are employed in nonradioactive DNA sequencing

techniques such as those developed by Prober et al (ref omitted) and Ansorge et al (ref ommitted) as well as for incorporation into hybridization probes (ref omitted). Fluorescent ddNTPs have also been used as terminal deoxynucleotidyl transferase substrates to label single (ref omitted) and double stranded DNA (ref omitted) (page 89, column 1, last sentence to page 89, column 2)". An ordinary practitioner would have been motivated to alter the dNTP dyes of Evangelista into ddNTP dyes in order to permit nonradioactive DNA sequencing, hybridization probe or terminal transferase methods to be used as expressly taught by Evangelista. An ordinary practitioner would have had a very high expectation of success since it is routine to make both dNTP and ddNTPs with the same label as discussed by Evangelista on page 89, column 2. It would have been further obvious to utilize the ddNTP resulting from this synthesis in a DNA sequencing method to yield a DNA which comprises the ddNTP.

10. Claims 1-3 and 9 are rejected under 35 U.S.C. 103(a) as being unpatentable over Evangelista et al in view of Tabor et al (U.S. Patent 5,614,365).

Evangelista teaches a compound of formula (I) (A-B-C) with a cyanine dye which meets the structural requirements of A, a linker of more than 10 atoms in length as required by B, and attached to the 5 position of dUTP, which has a triphosphate attached (page 91, figure 1). It should be noted, that because the attachment is at the 5 position, dUTP and dTTP yield identical structures. Evangelista further notes "Our DNA labeling results indicate that the distance provided by the 10-atom spacer arm between the pyrimidine ring and the rather bulky cyanine

label is sufficient to allow base pairing between the deoxyadenosine and deoxyuridine at the ends of the DNA fragments (page 97, column 1)".

Evangelista does not teach the use of a modified thermostable polymerase nor does Evangelista teach placement of the reagents into a kit.

Tabor teaches the use of modified thermostable polymerases in DNA sequencing reactions (column 5, lines 38-58). Tabor further teaches placement of the reagents into a kit (column 9, lines 57-62).

It would have been *prima facie* obvious to one having ordinary skill in the art at the time the invention was made to combine the fluorescently labeled ddNTPS which are made obvious by Evangelista into a kit with the modified thermostable polymerases of Tabor since Tabor notes "By modification of these enzymes using methods shown below, those in the art can now modify any desired thermophilic DNA polymerase to make it incorporate dideoxynucleotides more efficiently. Such enzymes will be superior to those existing in the present day for DNA sequencing both in automated machines and in manual sequencing, especially in procedures known as cycle sequencing (column 5, lines 46-53)". An ordinary practitioner would have been motivated to form a kit with ddNTPs as made obvious by Evangelista for the improved sensitivity of the dyes (page 96, column 2) as shown by Evangelista and for the use of a superior enzyme as expressly taught by Tabor. An ordinary practitioner would have been motivated to form a kit since with the use of a kit, one need not purchase gram quantities of multiple reagents, each of which is needed in only microgram amounts, when beginning a series of experiments. Further, the kit format

saves money and resources by dramatically reducing waste. The other advantage provided in a kit is quality control.

11. Claims 3, 4 and 9 are rejected under 35 U.S.C. 103(a) as being unpatentable over Evangelista in view of Haralambidis et al (Nucleic Acids Research (1987) 15(12):4857-4876).

Evangelista teaches a compound of formula (I) (A-B-C) with a cyanine dye which meets the structural requirements of A, a linker of more than 10 atoms in length as required by B, and attached to the 5 position of dUTP, which has a triphosphate attached (page 91, figure 1). It should be noted, that because the attachment is at the 5 position, dUTP and dTTP yield identical structures. Evangelista further notes "Our DNA labeling results indicate that the distance provided by the 10-atom spacer arm between the pyrimidine ring and the rather bulky cyanine label is sufficient to allow base pairing between the deoxyadenosine and deoxyuridine at the ends of the DNA fragments (page 97, column 1)".

Evangelista does not teach the specific linkers of claim 4.

Haralambidis teaches a linker (page 4860, figure 1) which is identical to the fourth claimed linker of claim 4, where the linker links to a nitrogen, as occurs in the structure of Evangelista.

It would have been *prima facie* obvious to one having ordinary skill in the art at the time the invention was made to combine the dye labeled compound rendered obvious by Evangelista with the linker of Haralambidis since Haralambidis states "In this paper we have described a method for the synthesis of C-5 substituted deoxyuridine nucleosides, with the substituent carrying a masked primary aliphatic amino group. This method is exceptionally mild and gives the

desired compound is high yield (page 4874)". Haralambidis further notes "It was found that oligonucleotides carrying a long (11 atom) linker arm to the fluorescein hybridize more efficiently to mRNA than those carrying a short (4 atom) arm (abstract, page 4857)". An ordinary practitioner would have been motivated to utilize the long linker arm of Harambidis in the synthesis of the cyanine dye of Evangelista for the expressly stated benefits of mild conditions, high yield and efficient hybridization.

Conclusion

12. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Jeffrey Fredman, Ph.D. whose telephone number is (703) 308-6568.

The examiner is normally in the office between the hours of 6:30 a.m. and 4:00 p.m., and telephone calls either in the morning are most likely to find the examiner in the office.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Gary Benzion, can be reached on (703) 308-1119.

Any inquiry of a general nature or relating to the status of this application should be directed to the Group receptionist whose telephone number is (703) 308-0196.

Papers related to this application may be submitted to Technology Center 1600 by facsimile transmission via the P.T.O. Fax Center located in Crystal Mall 1. The CM1 Fax Center numbers for Technology Center 1600 are either (703) 305-3014 or (703) 308-4242. Please note that the faxing of such papers must conform with the Notice to Comply published in the Official Gazette, 1096 OG 30 (November 15, 1989).

Jeffrey Fredman
Primary Patent Examiner
Art Unit 1637

February 25, 2002